that affects neurons in the mouse brain. When this group fed mice sucrose, they found that blood glucose peaked about 20 minutes afterwards. The change in blood glucose accompanying sucrose consumption also increased activity in the 'reward' neurons in the nucleus accumbens (the so-called 'pleasure' centre of the brain) when the taste defective mice licked the bottle they associated with reward. If changes in blood sugar are involved in the brain's evaluation of reward, the experiments by Burke and Waddell [2] suggest that these changes happen rapidly in flies, as the flies in their assay were able to recognize an odour based on the metabolic quality of its associated reward within a few minutes.

Whether the brain detects the metabolic quality of a consumed reward using glucose as the signal or whether this signal also involves other molecules like insulin [6,7] are mysteries yet to be solved. Intriguingly, fruit flies express gustatory receptors throughout their bodies [8], including their central brain neuropil structures. One receptor class, Gr28, has been found highly expressed in the suboesophageal ganglion [8], a structure involved in the regulation of feeding behaviour [9]. Post-ingestive signals could target the suboesophageal ganglion or act more directly on the circuits involved in establishing olfactory memories. For example, a fruit fly's long-term appetitive olfactory memories are established and maintained in a subset of neurons in the mushroom body [5,10]. If sugar receptors were expressed in these neurons, their activation by glucose could affect the protein-synthesis-dependent processes underlying long-term memory formation [11]. Alternatively, neurons projecting to the mushroom bodies could provide information about nutrient status to impact long-term memory consolidation [12].

These experiments collectively show that while sweet taste can facilitate rapid learning, lasting memories depend on whether or not the food reward had real value to the animal. The fact that both mice and flies need a metabolic reward to remember an odour-taste association may reflect conserved mechanisms in animals for behaviours involved in the regulation of feeding. This might have medical ramifications if the artificial sweeteners that we use by the tonne to sweeten our foods and drinks are only fooling our brains in the short-term. Surely every cake I've eaten before contained the real thing.

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# Cell Migration: Katanin Gives Microtubules a Trim

**New evidence suggests that katanin — best known for severing microtubules in their more stable regions — localizes at the leading edge of migratory cells and trims microtubules at their dynamic plus ends.**

**Peter W. Baas* and Vandana Sharma**

In recent years biological research has resulted in an expanding knowledge of the toolbox of proteins and mechanisms used by cells to get their work done. Cells of various types need to accomplish tasks such as division, migration, polarization, and extension of processes. Microtubules are instrumental to these various tasks, acting as architectural elements, force transduction elements, and also as railways for organelle transport. The ability of cells to rapidly reconfigure microtubules from one type of array into another, or to enable the microtubules to participate in complex processes, such as cell division or migration, requires proteins that very precisely take apart microtubules so that other proteins can then put them back together, as needed, and where needed. Studies have emerged from various laboratories on a category of enzymes called microtubule-severing proteins that hydrolyze ATP in order to break the lattice of the microtubule. In an exciting turn of events, a new paper now shows that katanin, the prototype microtubule-severing protein, can sever and/or depolymerize microtubules at their highly dynamic plus ends within

the leading edge of migratory cells [1].

Microtubule-severing proteins form hexamers that interact with the surface of the microtubule polymer, essentially grabbing and pulling at a tubulin subunit until the polymer gives way and breaks [2]. Early studies focused on microtubule-severing proteins as a means to release microtubules from the centrosome, so that they could move about the cytoplasm and populate other locales, such as the axons of neurons [3]. More recent studies have accentuated the power of microtubule severing to dramatically increase the number of microtubules in a cell or within a certain cellular region or apparatus, such as an axonal branch [4] or the meiotic spindle [5]. Interestingly, plant cells rely heavily on the severing of microtubules by katanin in order to re-craft their microtubule arrays during morphogenetic events [6]. Studies on spastin, another microtubule-severing protein, have demonstrated its central importance in neurons [7] as well as in cortical abscission in the final stages of cell division [8].

While never stated as a firm and fast rule, the general view has been that microtubule-severing proteins favor the more stable regions of microtubules over the more dynamic regions. This makes sense if one considers the purposes of microtubule severing to be as stated above. Cutting microtubules from the centrosome would be targeted more toward their minus ends, for example, which would presumably be more stable than the plus ends. Moreover, if the purpose of microtubule severing is to increase microtubule number, then the severing of highly dynamic microtubules would be futile as the resulting short microtubules would rapidly depolymerize. Cutting more stable microtubules, by contrast, would generate a population of stable short pieces that would resist depolymerization, and could be moved around in the cell and used as seeds for elongation into longer microtubules. This is what is thought to happen in both neuronal cells and plant cells [9].

In favor of this point of view, recent studies have shown that katanin strongly favors highly acetylated microtubules over less acetylated microtubules [10], and spastin strongly favors highly polyglutamylated microtubules over less polyglutamylated microtubules [11]. These post-translational tubulin modifications tend to accumulate in the more stable microtubules in cells, and serve as a 'code' for demarcating certain microtubules or certain regions along microtubules for interaction with various microtubule-related proteins [12]. The fact that the severing proteins interact more avidly with more highly modified microtubules suggests that severing of stable microtubules is preferred over the severing of more dynamic microtubules. In many cases, individual microtubules have more stable regions and more dynamic regions, and it would follow from these observations that the more stable regions would be preferred for severing by katanin. Given all of this, the idea of katanin trimming the plus ends of microtubules was not expected.

The new paper from the laboratory of David Sharp demonstrates convincingly that katanin is able to act as a powerful depolymerase in migrating *Drosophila* and human breast cancer cells. First, the authors showed that katanin is highly localized to the leading edge of these cells, which is a surprising result in itself given that katanin is more often localized at the centrosome [13] or dispersed throughout the cytoplasm of the various cell types that have been studied [14]. Second,

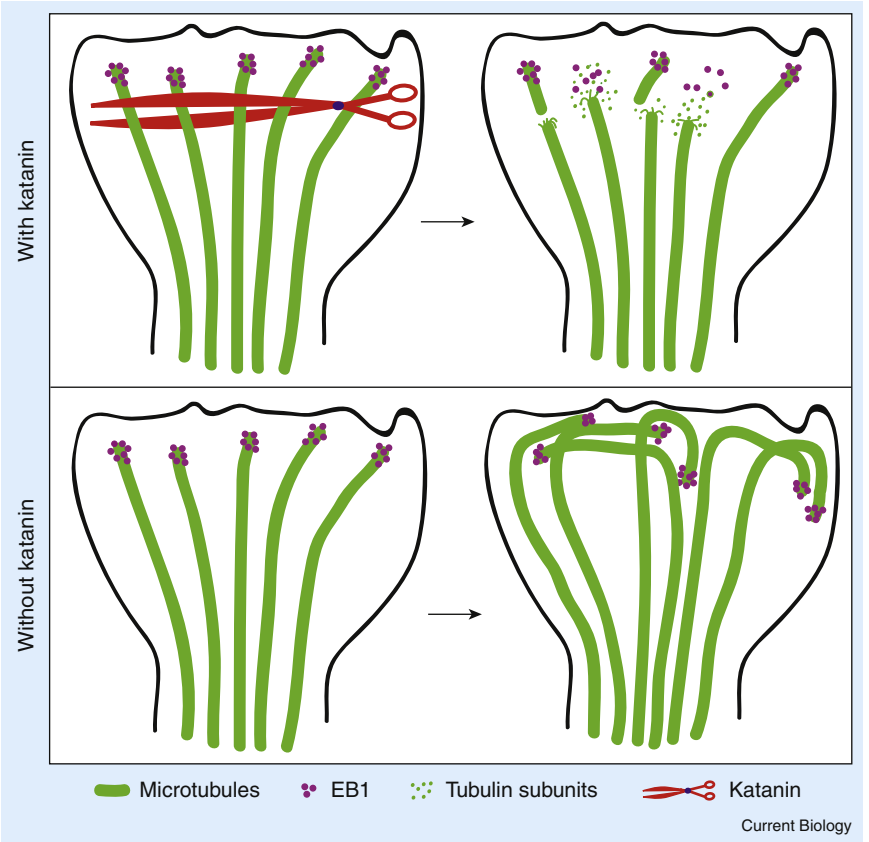


Figure 1. Schematic illustration of katanin's role in trimming microtubules at the leading edge of migratory cells.

Shown here are microtubules and tubulin (green tubes and dots, respectively), EB1 (magenta dots), and katanin (red scissors) in the leading edge region of a normal migratory cell with katanin intact (top panel) and in the same region of a migratory cell in which katanin has been experimentally depleted (bottom panel). In the normal case, katanin trims microtubules at their plus ends, allowing for appropriate microtubule behaviors during migration. In the absence of katanin, the microtubule ends are not trimmed and therefore over-assemble such that they bend along the edge of the cell and sometimes fold back on themselves. Interestingly, as detailed by Zhang *et al.* [1], the cell migrates faster when the microtubules are not trimmed back by katanin.

they showed that knocking down katanin results in a dramatic phenotype with the plus ends not pointed directly outward toward the leading edge, but rather with the microtubules folding over and extending parallel to the edge or even backward away from the leading edge. Thus, in these cells, without the activity of katanin, the microtubules do not maintain the required configuration to play their appropriate role in orchestrating cell migration (Figure 1). Third, the authors showed that the katanin-compromised cells move faster than controls, an entirely unexpected result, indicating that katanin-mediated regulation of microtubule organization and dynamics normally suppresses cell motility. This might be a potential avenue by which to develop clinical strategies for inhibiting metastasis.

The fact that katanin preferentially attacks microtubules from their plus ends *in vitro* (as reported by the authors) strongly indicates that it is not just katanin's localization at the cell cortex that accounts for its notable impact on the plus ends of microtubules in migrating cells. How might a preference for trimming microtubules at their plus ends be explained, in the light of other work suggesting a preference for severing of microtubules in their more stable regions? Interestingly, a biophysical paper published a few years ago put forth a compelling argument that katanin may preferentially sever microtubules at 'lattice defects' [15]. As a microtubule assembles, a consistent protofilament number along the length of the polymer is important for it to interact optimally with molecular motors and other microtubule-interacting proteins. Sometimes, a defect in the lattice can occur as the microtubule assembles, resulting in a small 'kink'. This might be, for example, as a result of 14 subunits comprising the diameter of the microtubule instead of 13. The idea that katanin might target lattice defects is appealing because it would provide cells with a mechanism for correcting such errors. One might imagine an inspector evaluating the work on a project and then demanding that an imperfect section be taken apart and corrected. The plus ends of microtubules could be viewed as the ultimate lattice defect, given how splayed and misshapen they are, compared with the tight, consistent lattice everywhere else along the polymer's length. Another way of looking at this would be that the plus end is simply the easiest or most vulnerable part of the microtubule to sever, given that the tubulin subunits are not as longitudinally attached here as they are elsewhere along the polymer's length. Thus, even though the plus end of the microtubule is the most dynamic part of the polymer and the part with the least post-translational modification, it may very well be a prime target for the severing proteins.

Over the years, cell biologists have been attracted to the idea that cells use a common toolbox to get their work done. In the microtubule compartment of the toolbox, there are molecular motors, stabilizers, severing proteins and various other types of proteins that influence the properties and behaviors of microtubules. The work of Zhang *et al.* [1] adds to a converging view that different cell types might reach for a different tool in order to get the same job done. For example, studies on fungal cells indicate that they can use kinesin-5 as a depolymerase [16], although kinesin-5 is almost universally used to influence microtubule movements in other cell types [17]. It now appears that some cell types may use katanin chiefly to cut microtubules in their more stable regions while other cells may use it to trim the plus ends of highly dynamic microtubules. Moreover, Zhang *et al.* [1] have conducted further experiments to develop a detailed model for how katanin coordinates with kinesin-13, a depolymerizing kinesin, as well as EB1, a microtubule plus-end-binding protein, to regulate microtubule behaviors at the leading edge. Not only does this work provide an exciting new twist in the microtubule field, but it prompts us to ponder just how creative cells might get in how they use their available tools.

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